REMARKS

Status of Claims and Amendment

Claims 13, 16, 18, 24, 27, and 29 have been amended. Claims 1-12 were previously canceled. Claims 13-29 are all the pending claims in the application. Claims 18 and 20-29 have been withdrawn by the Examiner as being directed to a non-elected invention. Claims 13-17 and 19 are rejected.

Claims 13 and 24 have been amended to even further clarify an isolated immunogenic, non-haemolytic *Actinobacillus pleuropneumoniae* (*App*) strain comprising at least one mutation in a transmembrane domain-encoding segment of the *apx*IA gene wherein the segment of the *apx*IA gene corresponds to nucleotides 886 to 945, nucleotides 697 to 759, or nucleotides 1105 to 1215 of SEQ ID NO. 1, and with or without at least one mutation in a transmembrane domain-encoding segment of the *apx*IIA gene, wherein the segment of the *apx*IIA gene corresponds to nucleotides 886 to 945, nucleotides 697 to 759, or nucleotides 1105 to 1215 of SEQ ID NO. 2. Support for the amendment to claim 13 may be found at least at page 3, lines 22-26, page 4, lines 23-32, Figure 1, and page 10, lines 11-28 of the specification.

Claims 16 and 27 have been amended to even further clarify that the deletion is of nucleotides 886 to 945 of SEQ ID NO. 1. Support for the amendment to claims 16 and 18 may be found at least at page 3, lines 22-26, page 4, lines 23-32, Figure 1, and page 10, lines 20-22 of the specification.

Claims 18 and 29 have been amended to even further clarify that the deletion is of nucleotides 886 to 945 of SEQ ID NO. 2. Support for the amendment to claims 16 and 18 may be found at least at page 3, lines 22-26, page 4, lines 23-32, Figure 1, and page 10, lines 23-28 of the specification.

The specification at page 13 has been amended to specify the address of the Depository recognized under the Budapest Treaty and designated in the specification, as well as the dates of deposit for CECT 5994 and CECT 5985 in compliance with 37 C.F.R. 1.804(a) and 1.809(d).[1] Applicants note that the deposited biological material fully meets the requirements of 37 C.F.R. §§1.802(a) and (b), §1.803(a), and §1.804(a), M.P.E.P. §2406.01, and §112, first paragraph, for written description and enablement.

No new matter is added.

Response To Elections/Restrictions

On page 2 of the Office Action, Applicants' election of the invention of Group I (claims 13-19) on November 1, 2007 is acknowledged.

The Office Action asserts that Applicants' argument with regard to Reimer is not persuasive because Reimer teaches mutations in the *apx*IA, *apx*IIA, and the *apx*ICABD operon and non-haemolytic strains. Further, the Office Action maintains that Groups I-IV have different technical features, as they relate to different strains.

In response, Applicants respectfully request withdrawal of the Restriction Requirement because, as discussed during the interview of July 1, 2009 and previously argued, the special technical feature shared by Groups I-IV is not disclosed by Reimer.

That is, Reimer does not disclose a mutant strain which comprises at least one mutation in a transmembrane domain-encoding segment of the *apx*IA gene wherein the segment of the *apx*IA gene corresponds to nucleotides 886 to 945, nucleotides 697 to 759, or nucleotides 1105

[1] In addition, Applicants note that copies of the original biological receipt of deposits for CECT 5985 and CECT 5994, the English translation of these original biological receipt of deposits, and a Statement of Availability for both CECT 5985 and CECT 5994 were filed June 12, 2008.

to 1215 of SEQ ID NO. 1, and with or without at least one mutation in a transmembrane domain-encoding segment of the *apx*IIA gene, wherein the segment of the *apx*IIA gene corresponds to nucleotides 886 to 945, nucleotides 697 to 759, or nucleotides 1105 to 1215 of SEQ ID NO. 2. Instead, Reimer discloses a wildtype strain (J45) which synthesizes and secretes exotoxins ApxI and ApxII, a mutant with the C, B, A, and D genes (*apx*ICABD operon) of ApxI completely deleted (mIT4-H), a mutant in which the deleted *apx*ICABD operon is restored (MIT4-H/pJFF800), and a mutant in which the B and D genes (*apx*IBD operon) for ApxI are restored.

Further, because Reimer concluded that an App mutant unable to export ApxI or ApxII is avirulent, i.e., deletion of the export B and D genes resulted in an avirulent mutant (see page 199, lines 19-21, and page 206, last paragraph of the conclusion of Reimer), there would have been no suggestion or guidance to lead one of ordinary skill in the art to make the presently claimed isolated immunogenic, non-haemolytic (avirulent) App strain. In fact, one of ordinary skill in the art would not have expected or predicted that introducing at least one mutation (e.g., deletion) in a transmembrane domain of the *apxIA* gene, with or without a mutation (e.g., deletion) in a transmembrane domain of the *apxIIA* gene would surprisingly result in:

- maintenance of the structure of ApxI and ApxII exotoxins,

- secretion of the ApxI and ApxII exotoxins,

- non-haemolytic activity,

- immunogenicity and

- immunoprotective characteristics.

Thus, the claimed isolated immunogenic, non-haemolytic (avirulent) App strain of the present invention is not disclosed or suggested in Reimer.

In addition, as discussed during the telephone interview of July 1, 2009, Applicants have amended claims 18, 24, 27, and 29 as suggested by Supervisor Mondesi to place the claims in condition for rejoinder. Also, with regard to withdrawn claims 20 (from which claim 21 depends) and claim 22 (from which claim 23 depends), Applicants have amended the specification to include the address of the Depository and dates of the deposit in compliance with 37 C.F.R. 1.804(a) and 1.809(d). Further, Applicants note that copies of the original biological receipt of deposits for CECT 5985 and CECT 5994, both made under the Budapest Treaty, the English translation of these original biological receipt of deposits, and a Statement of Availability for both CECT 5985 and CECT 5994 were previously filed June 12, 2008. Thus, the deposited biological material fully meets the requirements of 37 C.F.R. §§1.802(a) and (b), §1.803(a), and §1.804(a), M.P.E.P. §2406.01, and §112, first paragraph requirements for written description and enablement. As mentioned by the Supervisor during the interview of July 1, 2009, because the requirements for the deposits are met, i.e., the 112 requirements are satisfied, claims 20 (from which claim 21 depends) and claim 22 (from which claim 23 depends) should be in condition for rejoinder.

Withdrawal of the Restriction Requirement and rejoinder of claims 18 and 20-29 is respectfully requested.

Response To Claim Rejections Under 35 U.S.C. § 102(b)

1. MacInnes

Claims 13-17 and 19 remain rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 6,019,984 to MacInnes et al. ("MacInnes"), for the same reasons set forth in the

previous Office Action mailed September 17, 2008. For brevity, those reasons are not reiterated herein.

Although the Office Action acknowledges that MacInnes does not explicitly teach nucleotides 886 to 945 of *apx*IA gene, the Office Action takes the position that such a limitation would be inherent in the full sequence of *apx*IA taught in MacInnes.

Initially, Applicants note that the Office Action's rationale, which appears to form the basis of this rejection, that the limitation of nucleotides 886 to 945 of apxIA gene is inherently met by disclosure of the full sequence of *apx*IA in which the full transmembrane domains are included, is erroneous. This rationale ignores the requirement that all words in a claim must be considered in judging the patentability of that claim against the prior art, i.e., each and every limitation as set forth in the claim must be found in a single prior art reference. M.P.E.P. §2131 and §2143.03. In the present case, disclosure of the full sequence of *apx*IA does not explicitly or inherently meet the limitation of *at least one mutation* in a transmembrane domain-encoding segment of the *apx*IA gene, much more that the mutation(s) is in a transmembrane domain-encoding segment of the *apx*IA gene that corresponds either to nucleotides 886 to 945, to nucleotides 697 to 759, or to nucleotides 1105 to 1215 of SEQ ID NO. 1. Nor does the mere disclosure of the full sequence of *apx*IA meet the limitation of introducing at least one mutation in a transmembrane domain-encoding segment of the *apx*IA gene, as recited in claim 24.

Furthermore, as discussed during the interview of July 1, 2009 summarized in the Statement of Substance of Interview submitted herewith, and previously argued, MacInnes does not explicitly or inherently disclose the presently claimed invention for at least the following reasons. MacInnes is directed to a method of preparing a vaccine in which the microorganism has mutations in the transport genes (B and/or D) to obtain a mutant with at least one RTX toxin

that is substantially cell-associated, i.e., the toxin is not secreted because the B and/or D transport genes are inactivated (columns 13 and 14 of MacInnes). Further, "substantially cell-associated" as defined at column 8 in MacInnes is not a mutation. In this regard, MacInnes discloses that outer membrane proteins of *Actinobacillus pleuropneumoniae* can be altered by changing growth conditions (see column 21 and 22, Example 1), and that the quantity of cell-associated RTX toxin produced in culture is affected by the growth medium (column 23, lines 10-13).

In contrast, the presently isolated immunogenic, non-haemolytic *Actinobacillus pleuropneumoniae* (*App*) strain comprises at least one mutation in a transmembrane domain-encoding segment of the *apx*IA gene wherein the segment of the *apx*IA gene corresponds to nucleotides 886 to 945, nucleotides 697 to 759, or nucleotides 1105 to 1215 of SEQ ID NO. 1, and with or without at least one mutation in a transmembrane domain-encoding segment of the *apx*IIA gene, wherein the segment of the *apx*IIA gene corresponds to nucleotides 886 to 945, nucleotides 697 to 759, or nucleotides 1105 to 1215 of SEQ ID NO. 2.

Moreover, because MacInnes also reached the same conclusion as Reimer, that mutations in the transport genes (B and/or D) would inactivate the transport genes, and in MacInnes' case, result in a mutant with at least one RTX toxin that is substantially cell-associated (columns 13 and 14 of MacInnes), there would have been no suggestion or guidance to lead one of ordinary skill in the art to make the presently claimed isolated immunogenic, non-haemolytic (avirulent) App strain. In fact, it would have been unexpected and unpredictable that introducing at least one mutation (e.g., deletion) in a transmembrane domain of the *apxIA* gene, with or without a mutation (e.g., deletion) in a transmembrane domain of the *apxIIA* gene would surprisingly result in:

- maintenance of the structure of ApxI and ApxII exotoxins,

- secretion of the ApxI and ApxII exotoxins,

- non-haemolytic activity,

- immunogenicity and

- immunoprotective characteristics.

Thus, the claimed isolated immunogenic, non-haemolytic (avirulent) App strain of the present invention is not disclosed or suggested by MacInnes.

In addition, Supervisor Mondesi appeared to indicate, during the interview of July 1, 2009, that the arguments presented were persuasive to address the prior art rejections.

Reconsideration and withdrawal of the rejection under § 102(b) is respectfully requested.

2. Prideaux

Claims 13, 14, 15, 17 and 19 remain rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 6,472,183 to Prideaux et al. ("Prideaux"), for the same reasons set forth in the previous Office Action mailed September 17, 2008. For brevity, those reasons are not reiterated herein.

Specifically, the Office Action appears to have found Applicants' arguments, that none of the portions of Prideaux relied upon by the Office Action to support the rejection, namely, the Abstract, claims 1-4, columns 1-4, and any other portion of Prideaux, disclose the claimed strain comprising at least one mutation in a transmembrane domain, not to be persuasive. The Office Action appears to maintain the rejection because it is asserted that Example 4 of Prideaux teaches a mutated A gene of *apx*I in which the *apx*IA gene and Kanamycin resistant gene linked to a T5 promoter resulted in transformants resistant to Kanamycin.

In response, as discussed during the telephone interview of July 1, 2009 summarized in the Statement of Substance of Interview submitted herewith, and previously argued, Prideaux does not explicitly or inherently disclose the presently claimed invention.

Prideaux is directed to a modified APP strain comprising an RTX A gene and an inactivated RTX C gene, so that the C gene is mutated. Prideaux does not disclose at least one mutation in the transmembrane domain of the A gene of *apx*I or optionally *apx*II. Further, as previously argued, the transformants disclosed in Example 4 of Prideaux are *Escherichia coli* transformants expressing a wild-type *apx*IA gene. Clearly, such is not even an *Actinobacillus pleuropneumoniae* strain, much more an isolated immunogenic, non-haemolytic *Actinobacillus pleuropneumoniae* strain comprising at least one mutation in a transmembrane domain-encoding segment of the *apx*IA gene wherein the segment of the *apx*IA gene corresponds to nucleotides 886 to 945, nucleotides 697 to 759, or nucleotides 1105 to 1215 of SEQ ID NO. 1, and with or without at least one mutation in a transmembrane domain-encoding segment of the *apx*IIA gene, wherein the segment of the *apx*IIA gene corresponds to nucleotides 886 to 945, nucleotides 697 to 759, or nucleotides 1105 to 1215 of SEQ ID NO. 2.

Further, because Prideaux only mutated the C gene in order to obtain a modified APP strain comprising an intact RTX A gene and an inactivated RTX C gene, there would have been no suggestion or guidance to lead one of ordinary skill in the art to make the presently claimed isolated immunogenic, non-haemolytic (avirulent) App strain. In fact, it would have been unexpected and unpredictable that introducing at least one mutation (e.g., deletion) in a transmembrane domain of the *apxIA* gene, with or without a mutation (e.g., deletion) in a transmembrane domain of the *apxIIA* gene would surprisingly result in:

- maintenance of the structure of ApxI and ApxII exotoxins,

- secretion of the ApxI and ApxII exotoxins,

- non-haemolytic activity,

- immunogenicity and

- immunoprotective characteristics.

Thus, the claimed isolated immunogenic, non-haemolytic (avirulent) App strain of the present invention is not disclosed or suggested by Prideaux.

In addition, Supervisor Mondesi appeared to indicate, during the interview of July 1, 2009, that the arguments presented were persuasive to address the prior art rejections.

Reconsideration and withdrawal of the rejection under § 102(b) is respectfully requested.

Response To Claim Rejection Under 35 U.S.C. § 112 for Indefiniteness

Claims 13-17 and 19 are rejected under §112, second paragraph as being allegedly indefinite for the following reasons.

First, the recitation in claim 13 "wherein the transmembrane domain-encoding segment in each *apx*IA and *apx*IIA gene corresponds either to nucleotides 886 to 945, to nucleotides 697 to 759, or to nucleotides 1105 to 1215" is allegedly unclear because a sequence identifier should be recited for the specific nucleotides.

Second, the term "optionally" in claim 13 is allegedly unclear because it is not defined in the claim, the specification does not provide a standard for ascertaining the requisite degree, and the scope is not readily understood by one of ordinary skill in the art.

In response, and solely to advance prosecution of the present application, claim 13 has been amended to further clarify that the claimed isolated immunogenic, non-haemolytic *Actinobacillus pleuropneumoniae* (*App*) strain comprises at least one mutation in a

transmembrane domain-encoding segment of the *apx*IA gene wherein the segment of the *apx*IA gene corresponds to nucleotides 886 to 945, nucleotides 697 to 759, or nucleotides 1105 to 1215 of SEQ ID NO. 1, and with or without at least one mutation in a transmembrane domain-encoding segment of the *apx*IIA gene, wherein the segment of the *apx*IIA gene corresponds to nucleotides 886 to 945, nucleotides 697 to 759, or nucleotides 1105 to 1215 of SEQ ID NO. 2. Claim 16 has also been amended to recite that the "deletion is of nucleotides 886 to 945 of SEQ ID NO. 1" to be consistent with the amendments of claim 13.

In addition, claim 18 has been amended to recite that the "deletion is of nucleotides 886 to 945 of SEQ ID NO. 2" to be consistent with the amendments of claim 13. Claim 24 has also been amended in a similar manner as claim 13, and claims 27 and 29 have been amended in a similar manner to claims 16 and 18 to keep consistent with the amendments to claim 24.

As discussed during the interview of July 1, 2009, Supervisor Mondesi stated that he believes the claim amendments should be sufficient to overcome the §112, second paragraph rejection.

Reconsideration and withdrawal of the rejection under §112, second paragraph, is respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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Date: July 14, 2009